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Gastrointestinal Stromal Tumors

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. They typically arise in the stomach, but can also be found in the small intestine, colon, rectum, and uncommonly in the esophagus and omentum. They are estimated to have an incidence of 10 to 20 cases per 1 million population, of which approximately one third are deemed malignant [1,2]. In the past, these tumors were commonly termed leiomyomas or leiomyosarcomas and had a reputation for poor prognosis. Disease commonly recurred in the peritoneum or metastasized to the liver. The mainstay of therapy was surgery with little documented efficacy of standard chemotherapeutic agents [1,3].

The outcome and prognosis for patients who have GISTs has changed with the identification of *KIT*, a type III tyrosine kinase receptor [4], as the biologic driver of the tumor [1,5,6]. During embryologic development, KIT is important for hematopoiesis, melanogenesis, gametogenesis, and mast cell growth and differentiation [7,8]. KIT is required for the development of the interstitial cells of Cajal (ICC), which are the pacemaker cells of the gut [9,10]. It is believed that ICC or their precursors are transformed by an oncogenic mutation in *KIT* [11,12]. Although most GISTs will express KIT, a minority will be negative for KIT or contain a wild-type gene for KIT [13]. Some of the wild-type *KIT* or KIT-negative tumors have been shown to contain *PDGFR-α* (platelet-derived growth factor receptor–α) mutations [14,15]. Mutations in *KIT* or *PDGFR-α* lead to constitutive activation of the kinases, resulting in continued growth and cell division, thus driving tumor growth. The presence of KIT and PDGFR-α recep-

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tors provide the rationale for testing of inhibitors of these tyrosine kinases. However, imatinib is ineffective in other cancers that express KIT, such as small-cell lung cancer, seminoma, and Ewing sarcoma, perhaps related to the lack of mutated *KIT* in these tumors. The efficacy of imatinib mesylate has significantly improved the outcome for patients who have metastatic and unresectable GISTs [16,17]. The agent is now being tested in the adjuvant and neoadjuvant settings. In addition, several agents are being tested for the treatment of patients who are refractory to or intolerant of imatinib.

Surgical management of gastrointestinal stromal tumors

Preoperative assessment

Percutaneous biopsy of a suspected GIST is not recommended because the tumors are often fragile, especially if large or there is extensive intratumoral hemorrhage or necrosis. Instead, endoscopic techniques for evaluation and tissue procurement should be considered for accessible tumors. In the initial evaluation of biopsy-proven GISTs, contrast-enhanced CT is the preferred imaging modality to determine stage of disease. Functional imaging with 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) can complement standard CT by assisting with differentiation of benign from malignant tissue, necrotic scar tissue from active tumor, and nondescript benign changes from tumor [18,19]. Most GISTs demonstrate high glycolytic activity at baseline before imatinib therapy. Following the initiation of imatinib therapy, 80% of patients will demonstrate response based on PET images, which can occur within hours after a single dose of imatinib. Therefore, baseline PET scans should be considered before initiation of imatinib, or even surgical exploration if future treatment with imatinib is likely.

Primary disease

Clinically, GISTs range from small indolent tumors curable with surgery alone to aggressive cancers, but all should be regarded as having malignant potential. Complete surgical resection without rupture remains the primary treatment modality. The objective of surgery is removal of all gross tumor which, depending on factors such as location, size, and extent, may require subtotal, total, or even en bloc organ resection. Wide margins are not generally necessary for disease clearance. Systematic lymphadenectomy is also unnecessary because regional lymph node involvement is rare in GIST. In general, the standards for organ resection, organ preservation, and reanastomosis should govern the surgical resection techniques for GISTs. In contrast to other invasive intra-abdominal malignancies, gastric-based GISTs often protrude from the stomach, displacing surrounding structures. Complete resection can be accomplished in 40% to 60% of all patients who have GIST and in more than 70% of those who have primary, nonmetastatic disease [5,20–22].

Successful use of laparoscopic techniques for the resection of primary GIST has been reported in small individual series [23,24]. Tumors were small (3 cm), localized, and typically characterized as being benign or of low-grade malignancy. One group that used laparoscopic wedge resection to treat 34 patients who had submucosal tumors of the stomach, including 14 GISTs, reported no disease recurrences over a 5-year follow-up period. However, long-term data for patients who have undergone laparoscopic resection for GISTs are generally lacking, and the number of GIST patients in published cases or series is small.

Outcomes

The published results of surgical resection for primary GISTs have several limitations. First, most of the series contain few patients because the disease is uncommon, and therefore the experience at a single institution is limited. To compensate for the small numbers, investigators often analyze primary disease in conjunction with recurrent or metastatic disease. Results are also confounded by the inclusion of patients who have other intra-abdominal sarcomas (leiomyosarcoma in particular) because of the previous difficulties in the diagnosis and classification of GISTs. Furthermore, GISTs exhibit a remarkably wide spectrum of clinical behavior. Despite the recognition that certain morphologic features portend a more aggressive behavior, it remains difficult to predict the likelihood that a GIST will metastasize or recur following complete resection.

Very low risk GISTs have an excellent prognosis after primary surgical treatment, with over 90% 5-year survival. Evidence from long-term follow-up of patients who have undergone surgical resection of a high-risk GIST indicates that surgery alone is generally not curative. Before the introduction of imatinib, these tumors had an extremely poor prognosis even after surgical resection, with median survival of 12 months. As many as 85% to 90% had an adverse outcome, including recurrence, metastasis, or death [25]. In general, local recurrences or metastases develop in approximately half of patients who have potentially curative operations for GISTs, regardless of the site of the primary tumor, and 5- and 10-year survival rates after potentially curative surgery are 32% to 78% and 19% to 63%, respectively [26]. The median disease-specific survival for patients who have primary GISTs is approximately 5 years. Outcomes reported in recent studies are consistent with those in earlier series (Table 1).

Table 1
Major surgical series of CD117 + gastrointestinal stromal tumors

Reference	Patients	Site (%)	Localized disease at presentation (%)
De Matteo et al [6]	200	G (39), SB (32), C (15), O (13)	46
Pidhorecky et al [20]	71	G (45), SB (45), C (10)	56
Pierie et al [22]	69	E (1), G (39), SB (23), C (16)	51

Abbreviations: C, colonic; E, esophageal primary site; G, gastric; O, omental; SB, small intestinal.

Perforation or tumor rupture and the presence of residual gross disease are among the main factors portending an adverse outcome in patients who have undergone GIST resection. Incomplete tumor excision is associated with a significantly reduced disease-free and overall survival compared with complete resection. For patients who had complete GIST resections, 5-year survival rates of 42% have been reported, with 8% to 9% reported for those who had incomplete resections. In an analysis of 17 patients who had primary gastric stromal sarcomas, overall median survival was 19 months, compared with a median survival of 39 months after complete removal of the tumor. Tumor rupture eliminates the survival advantage conferred by complete resection of a nonlocally advanced primary GIST. In one study, it reduced the median survival from 46 to 17 months, which was comparable to the median survival after incomplete resection (21 months). Partial resection for palliative purposes is justifiable in patients whose overall performance status is good and who would benefit from the relief of symptoms related to obstruction or bleeding.

Recurrent or metastatic gastrointestinal stromal tumors

Outcomes in patients who had metastatic GISTs and in those who had GIST recurrence after primary resection were usually extremely poor in the era before imatinib; the median survival of such patients generally ranged from 6 months to approximately 18 months. After resection of the primary tumor, most patients subsequently recur. In some cases, tumor rupture can account for the recurrence, particularly if it occurs in the peritoneum. However, in most patients, recurrence develops after what seemed to be a curative resection. Strikingly, only 13 (10%) of 132 patients who underwent complete resection of the primary tumor were disease-free after a median follow-up of 68 months in the M. D. Anderson Cancer Center series [27]. The median time to recurrence is approximately 1.5 to 2 years. The first site of recurrence in GIST is typically within the abdomen and involves the peritoneum, the liver, or both. In the Memorial Sloan-Kettering Cancer Center (MSKCC) report, 27 patients who had complete resection of their primary tumor at MSKCC were followed up prospectively and had an assessable first recurrence. The first recurrence involved the peritoneum in half of the patients and the liver in nearly two thirds of the patients. Surgical resection may be beneficial in some patients who have GISTs who develop peritoneal recurrence. Unfortunately, what appears as limited intraperitoneal disease on preoperative radiologic imaging often turns out to be numerous nodules, if not frank sarcomatosis, at laparotomy. Recurrent tumors will be limited to the region of the primary tumor (25%) or located diffusely throughout the abdomen. It is uncommon to find extra-abdominal spread to the regional lymph nodes, lungs, bones, or subcutaneous sites. The liver is the sole site of recurrence or metastasis in approximately 40% to 50% of patients. As with primary GISTs, recurrent peritoneal nodules tend to rest on the surface of the intestine, omentum, mesentery, or abdominal wall and do not significantly invade the surrounding structures. Therefore, they can often be removed with limited resections.

Approximately half of patients presenting with first recurrence are amenable to surgical resection.

Results of surgical management of GIST recurrence or spread have been variable, depending on such factors as the stage of disease, tumor risk profile, and length of the disease-free interval after initial resection. In some patients whose primary tumor was a very-low-risk or low-risk rectal or anal GIST, locally recurrent disease has been treated successfully with total excision without further recurrence from 4 to more than 10 years. In their study of 239 GISTs, Clary et al [28] analyzed outcomes after resection of primary, locally recurrent, or metastatic GISTs. Complete resection was associated with improved disease-specific survival in all cases: 96 versus 26 months for primary disease, 49 versus 8 months for locally recurrent disease, and 39 versus 11 months for metastatic tumor.

Mudan et al [29] reported a median survival of 15 months after surgery for recurrent GIST. The longest survival was observed in patients whose recurrence consisted of hepatic metastasis alone. In this study, the only significant determinant of survival was the duration of the disease-free period between initial surgery and GIST recurrence, an indicator of the biologic aggressiveness of the tumor. In another study of 56 patients (34 who had GISTs or gastrointestinal leiomyosarcomas) who underwent complete resection for liver metastasis of sarcoma, an interval more than 2 years between diagnosis of the primary tumor and development of the metastasis was found to be a significant predictor of survival after hepatectomy. Complete resection of hepatic metastases was associated with prolonged survival in this study.

When the clinical presentation suggests that a patient who has recurrent GISTs might be a candidate for surgery, comprehensive diagnostic imaging is required for preoperative staging. In most cases, CT is satisfactory for the demonstration of GISTs in the liver, although MRI affords greater sensitivity for small lesions. PET is proving to be a sensitive staging tool and may be useful in identifying imatinib-resistant lesions. Complete surgical resection should be attempted in selected patients whose recurrent or metastatic disease is localized in a single site (eg, liver) or consists of low-volume, multiple-site lesions on the peritoneal surfaces. Resection of multiple intra-abdominal organs and tumor debulking are not warranted, except perhaps for palliation of localized bleeding or obstruction in patients whose performance status is otherwise excellent. Surgery for recurrent or metastatic GISTs is contraindicated in patients who have poor performance status and significant comorbid disease.

Unfortunately, resection of recurrent peritoneal GIST is seldom curative, even when all gross tumor is removed. Before the introduction of imatinib, adjuvant intraperitoneal chemotherapy using mitoxantrone was evaluated as a strategy for treating peritoneal recurrence of GIST following resection or debulking [30]. Nearly one third of patients harbored liver metastases in addition to their peritoneal disease burden. Treatment did not influence survival in patients who also had hepatic metastases; however, the median time to subsequent recurrence after therapy in patients who had disease isolated to the peritoneum was increased from 8 months in eight patients who had surgery alone to 21 months in 19 patients

who had surgery and intraperitoneal mitoxantrone. The 2-year actuarial survival in these groups was 0% and 33%, respectively. This treatment concept has been largely supplanted because of the clinical efficacy of imatinib. Palliative use of chemoembolization for liver metastases has been effective in temporary control of lesions [31]. Newer approaches with radiofrequency ablation and or cryosurgery at the time of surgical debulking have also been reported [32].

Emerging approaches to combining imatinib and surgery

The possibility of cure afforded by surgery provides a rationale for using imatinib in conjunction with surgery. The role of imatinib as an adjuvant treatment to prolong disease-free survival and improve overall survival is being tested in several studies internationally. In addition, neoadjuvant imatinib to debulk tumors is also being evaluated in a phase 2 clinical trial led by the Radiation Oncology Therapy Group. Imatinib treatment in patients who present with inoperable malignant GISTs might enable them to undergo successful resection after a reduction in tumor size or spread. Pharmacologic debulking with imatinib may also be a strategy to optimize the timing of surgery and avoid emergency operations, with the attendant risk for complications, particularly in patients who have large GISTs that predispose them to hemorrhage or tumor rupture. In addition, neoadjuvant imatinib may allow a marginally respectable GIST to be resected, but requires close follow-up by the surgeon and medical oncologist for signs of response or growth on imatinib. Surgical resection of imatinib unresponsive lesions has been performed. There appears to be a greater operative risk in patients who have nonresponsive disease compared with patients who have some response to imatinib [33].

It is conceivable that if imatinib can improve the outcome of surgery, surgery might enhance the results of imatinib therapy. The extent to which strategies combining the use of imatinib and surgery in treating GISTs are feasible in actual practice awaits elucidation in clinical trials.

Medical management of gastrointestinal stromal tumors

Before targeted molecular therapies

GISTs are refractory to standard chemotherapy. Until recently, few studies separated GISTs from other sarcoma histologies. Edmonson and colleagues [34] conducted a trial of dacarbazine, mitomycin, doxorubicin, and cisplatin and enrolled two cohorts of patients: those who had leiomyosarcomas and those who had GISTs. The response rates contrasted sharply with a 54% response rate in leiomyosarcomas compared with 4.9% response rate in GISTs. In addition, 0% to 27% GIST response rates have been reported for regimens containing doxorubicin and ifosfamide 7% for those containing paclitaxel, and 0% for those containing gemcitabine [1]. One potential explanation for the lack of effective-

ness of standard chemotherapeutic agents on GISTs is enhanced expression of multidrug-resistant proteins compared with leiomyosarcomas [35]. The limited response rates of these therapies were associated with poor survival in patients who had metastatic disease.

Targeted therapy: imatinib mesylate

The identification of *KIT* and *PDGFR-α* as the oncologic drivers of GISTs provided targets for therapy [3,36]. Imatinib mesylate, an oral tyrosine kinase inhibitor with activity against Abl, Bcr-Abl, KIT, and PDGFR [37,38], was hypothesized to lead to clinical benefit in GIST. Preclinical data demonstrated activity against wild-type and mutant forms of KIT [38,39]. Phase 1 testing demonstrated efficacy of the agent in GIST patients who had a maximum tolerated dose of 400 mg twice daily [16,40]. Dose-limiting toxicities were nausea, vomiting, edema, and rash, with the most common toxicities from GIST clinical trials summarized in Table 2. Hematologic toxicities were more frequent in stud-

Table 2
Toxicity profile of patients receiving imatinib

	Phase 1, N = 40 (4 non-GIST) [16]	Phase 2, N = 198 (24 non-GIST) [17,41]	Phase 3 (EORTC), N = 972 [42]	Phase 3 (United States), N = 458 [43]	
Side effect	≥Grade 2	≥Grade 3	≥Grade 3	≥Grade 3	
Nausea	18%	5%	3%	Gastrointestinal[a]	14%
Vomiting	18%	5%	3%		
Diarrhea	NR	5%	3%		
Edema	25%	5%	6%	Cardiovascular	9%
Rash	13%	10%	4%	Dermatologic	5%
Bleeding, including intratumoral	8%	6%	5%	7%	
Anemia	NR	10%	12%	Hematologic[b]	19%
Leukopenia	NR	3%	3%		
Granulocytopenia	NR	10%	7%		
Neutropenic fever	3%	NR	NR		
Infection	NR	NR	4%	4%	
Fatigue	NR	NR	8%	NR	
Dyspnea	3%	NR	4%	Lung	2%
Pleuritic pain	NR	6%	6%	Pain[c]	8%
Abdominal pain	NR	3%	NR		
Liver function abnormalities	NR	3%	NR	3%	
Anorexia	NR	3%	NR	NR	
Flu-like symptoms	NR	NR	NR	6%	

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; NR, not reported.

[a] Encompasses nausea, vomiting, and diarrhea.

[b] Encompasses anemia, leukopenia, granulocytopenia, and neutropenic fever.

[c] Encompasses pleuritic pain and abdominal pain.

ies of imatinib in chronic myelogenous leukemia (CML) likely because of leukemic cell involvement of the bone marrow in CML [44,45]. In addition, the frequency of bleeding in GIST patients was greater likely because of bleeding with tumor response, particularly in the early trials of the drug when many patients had multiple bulky metastases. Factors impacting on toxicity have been evaluated with low hemoglobin correlating with hematologic toxicity, and low albumin correlating with development of edema and fatigue. Higher dose was correlated with edema, fatigue, rash, and dyspnea [19].

The trials of imatinib rapidly proceeded from phase 1 to phase 3 because of the unprecedented activity of the agent and the need to treat patients who were without other therapeutic options [16,17,40,41–43]. The phase 1 trials tested 400 mg, 300 mg twice a day, 400 mg twice a day, and 500 mg twice a day, with the latter dose identified as dose limiting [16,40]. The US-Finland trial, initiated before the completion of the phase 1 trial, tested 400 mg and 600 mg [17,46]. Although over 100 patients were treated, the study was not powered to determine superiority of one dose level over the other. A second phase 2 trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) evaluated 400 mg twice a day in GIST and non-GIST patients [41]. Lastly, the two large international phase 3 trials assessed 400 mg daily compared with 400 mg twice a day.

The compiled response rates (Table 3) are comparable in the phase 1 and 2 studies but have slightly lower response rates noted in the phase 3 trials. The phase 1 and 2 trials in patients who had GIST had partial response rates of 54% to 71%, with an additional 17% to 37% with stabilization of disease. Patients who had symptomatic bulky disease noted rapid improvement in clinical symptoms correlating with the loss of metabolic activity seen by FDG-PET scanning [18,47]. Objective responses by CT scanning were reported up to 1 year after starting imatinib. However, earlier indications of response can be seen using tumor nodule density changes [48]. What is clear from these data is that imatinib, although effective, does not lead to many complete responses. Despite this fact, most patients benefit from imatinib, with 79.5% to 91% obtaining objective responses or prolonged stable disease. An analysis of the US-Finland trial found that patients who had stable disease as their best response to treatment had similar survival to patients who achieved partial or complete responses (Fig. 1) [49].

Table 3
Response to imatinib in metastatic and unresectable gastrointestinal stromal tumors

Response in KIT + GIST	Phase 1, N = 36 [16]	Phase 2, N = 174 [41,49]	Phase 3, N = 1673 [42,50]
Complete response	0%	1%	4%
Partial response	54%	71%	45%
Stable disease	37%	17%	28%
Progressive disease	9%	13%	21%
Not evaluable	0%	4%	4%

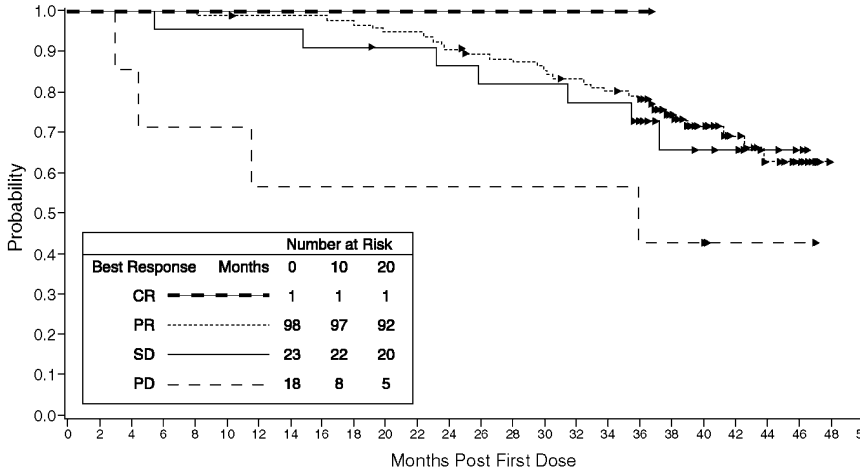

Fig. 1. Kaplan-Meier estimate of survival for patients treated on the US-Finland phase 2 trial. Patients whose response was unknown (N = 7) are not included. (Courtesy of Novartis, Basel, Switzerland; with permission.)

The phase 3 trials conducted in North America, Europe, and Australia rapidly accrued close to 1700 patients in 9 months. Both studies documented an increase in grade 3 and 4 toxicities in patients treated with 400 mg twice a day [42,43], although this was mitigated in the patients who began at 400 mg daily and then had their dose escalated to 400 mg twice a day at the time of disease progression [42]. Fatigue and anemia were more severe when switching from 400 mg daily to 400 mg twice daily, in contrast to neutropenia that decreased in incidence.

The lower response rates noted in the multicenter phase 3 trials are not unanticipated given the multiple investigators participating. However, the two studies arrived at slightly different conclusions. The North American trial, S0033, was powered to determine if one dose was superior to the other in terms of overall survival and enrolled 746 patients [43]. In contrast, the EORTC-led trial had as its primary endpoint progression-free survival and enrolled 946 patients. The EORTC-led trial documented an advantage to initiation of imatinib at 400 mg twice a day over 400 mg daily in terms of progression-free survival, without any difference in overall survival [42]. The North American trial found no statistical difference in the overall survival and progression-free survival between 400 mg and 400 mg twice a day [43,50]. The reasons for the differences in these conclusions are not clear. One possible explanation is that if the North American trial had accrued a larger number of patients, the same difference in progression-free survival would have been seen. However, there are other possible explanations. First, there may have been differences in the manner in which dose reductions and delays occurred between the two studies that affected the amount of the drug patients actually received in each study. Secondly, as discussed later,

response to imatinib is correlated with mutation site in *KIT* and *PDGFR-α*. Therefore, differences in the distribution of the mutations sites in the low- and high-dose cohorts could result in a change in response rate and progression-free survival. Mutation analyses are being performed retrospectively and will be available in the future.

The length of imatinib treatment in patients who have advanced nonresectable or metastatic GISTs is the focus of a trial being conducted by the French Sarcoma Group [51]. This phase 3 trial randomized patients who have stable disease (SD), partial response (PR), or complete response (CR) following 12 months of treatment to stopping or continuing imatinib therapy. The primary endpoint of the study was to assess progression-free survival with secondary endpoints to assess overall survival and response to the re-initiation of imatinib in patients who discontinued imatinib. This study was the first to enroll patients who were not only KIT-positive by immunohistochemistry, but also patients who had KIT-negative GISTs with evidence of *PDGFR-α* mutations. The study was powered to detect a 10% to 25% difference in progression free survival (PFS) at 3 months. An interim analysis was performed in May 2004 on 48 of the 58 patients who had undergone randomization and for whom there was more than a 1-year follow-up. Of these, ten of the 25 patients whose imatinib was discontinued had progressed in contrast to none of the patients who were on continuous therapy. The median progression-free survival was 6 months in the patients who stopped imatinib, with 90% of the patients responding to the re-introduction of imatinib. Based on this interim analysis, further randomization was discontinued.

Determinants of response to imatinib therapy

Analysis of mutation site and response to imatinib in GISTs is relevant for a drug that binds KIT [4,12,52–55] and PDGFR-α [14,15] to inhibit their function. In vitro, all *KIT* mutations appear to be sensitive to imatinib, although mutations in exon 18 of *PDGFR-α* are not sensitive [56]. The largest reported series of clinical samples correlating tumor mutations with response comes from the US-Finland trial (see Table 3) [57]. Tumors were screened for mutations in the sites known to commonly contain mutations: *KIT* exon 9, 11, 13, and 17, and *PDGFR-α* exon 12 and 18. Of 127 samples, 93% percent were found to contain mutations, predominantly in *KIT* (95%) with few in *PDGFR-α* (5%). Most mutations were in *KIT* exon 9 or exon 11. Tumors with *KIT* exon 11 mutations had the highest partial response rates and survival, followed by tumors with *KIT* exon 9 mutations, followed by those tumors with no detectable mutations in *KIT* or *PDGFR-α*. There were too few patients who had *PDGFR-α* mutations or *KIT* exon 13 or 17 mutations to analyze.

Another factor that has become increasingly apparent in the management of patients who have GISTs and treated with imatinib is the differences in how this tumor responds radiographically compared with many other malignancies. There is a strong correlation with tumor response by FDG-PET scanning observed

rapidly in the treatment course. Using standard response evaluation criteria in solid tumors (RECIST) criteria, achieving a partial response takes significantly longer. Lastly, response and progression can occur without evidence of significant change in the size of tumor lesions [48]. CT scans detect early changes in tumor density that precede the change in size of lesions. In addition, the growth of more solid areas can be detected within a lesion that represent outgrowth of a resistant clone of tumor cells. Recognizing the limitations of standard response criteria is crucial in the assessment of patients who have GISTs and are receiving imatinib.

Progression of gastrointestinal stromal tumors on imatinib

Clinical spectrum

There are two patterns of resistance to imatinib that are observed in patients who have GISTs. The first is a small group of patients who progress rapidly and never benefit from imatinib; the 9% to 17% of patients on imatinib trials who have progressive disease (PD) as their best response [16,17,42,43]. One possibility is that these patients did not have GIST, but another sarcoma with KIT expression. Many of the trials have incorporated expert pathologic review and genotyping of these tumors to minimize this possibility. In addition, response to imatinib varies based on the site of mutation.

The second cohort of patients are those who have been maintained on imatinib with an initial stabilization or response of their disease for more than 3 months, who then develop progression [16,42,43,58]. The median time to progressive disease is 18 to 24 months. This second group often has an increase in the size of some lesions, but not commonly all sites of disease; this is in marked contrast to the first cohort in whom all sites of disease progress. The cause of resistance at this time is not entirely clear. Mechanisms hypothesized to be of importance are the loss of KIT inhibition as a consequence of increased drug efflux or other pharmacokinetic factors, KIT amplification/deletion, or additional *KIT* mutations. Alternatively, KIT inhibition may still be present and then a second genetic mutation would be suspected. The 30% to 35% incidence of tumor stabilization/response to dose escalation in patients started at 400 mg daily of imatinib is indirect data suggesting that drug efflux mechanisms or pharmacokinetic factors may contribute to progression. To date, there are no reports of gene amplification of *KIT* or *PGDFR-α* as an alternate reason for the effectiveness of increasing drug dosage. There are increasing reports of metastatic lesions with additional mutations in *KIT* or *PGDFR-α* [59], and this appears to be the primary mechanism of resistance. It is not clear at this time if the development of secondary mutations develops under the selection pressure of imatinib or if these areas represent clonal outgrowth of a preexisting tumor cell with two mutations. Understanding the biologic mechanisms of resistance is important, as these patients will increasingly provide therapeutic challenges.

Clinical management of imatinib resistance

The initial question that needs to be assessed in patients who have progressive disease is the feasibility of surgical debulking of progressive lesions. Clearly, patients who are likely to benefit the most are those who have isolated progression and not those who have diffuse progression. Alternative palliative approaches include chemoembolization or radiofrequency ablation of liver metastases. Increasing the dose of imatinib in patients who have progressed on 400 mg daily is also an appropriate option, as it would be anticipated that up to 30% to 35% of patients would derive benefit with stabilization or response of their disease [45,50]. However, patients have had their doses of imatinib escalated above 400 mg twice a day without clear data on its benefits. Referral for clinical trial options is an additional option (Table 4). Lastly, for patients who are not candidates for the above measures and who do not qualify for experimental approaches, continuation on imatinib at a dose that is well tolerated is of benefit despite progression. Clinical trials that have stopped imatinib therapy before the initiation of alternate therapies have demonstrated increases in clinical symptoms and tumor flare by PET scan [60,61]. Thus, using imatinib until oral intake is no longer feasible is recommended.

SU011248

The agent with the greatest clinical experience to date is the multitargeted tyrosine kinase inhibitor SU011248 with activity against KIT, PDGFR, VEGFR (vascular-endothelial growth factor receptor) 1 and 2. Phase 1 testing of this agent evaluated various doses and schedules including: 25 mg, 50 mg, or 75 mg orally once daily for 14 days, followed by a 14-day rest period per cycle; 50 mg orally for 14 days with 7 days rest; and 50 mg orally for 28 days with 14 days rest. The latter schedule was selected for testing in the phase 2 and ongoing phase 3 trial in GISTs. Toxicities included: fatigue, nausea, vomiting, asymptomatic transient increases in lipase and amylase, uncomplicated neutropenia, hypertension, hand-foot syndrome, anemia, and bleeding at site of tumor biopsies. In addition, patients who had a history of coronary artery disease were found to have asymptomatic cardiac enzyme elevations.

Table 4
Therapeutic agents in clinical development for gastrointestinal stromal tumors

Agent	Targets	Phase of testing
SU011248	KIT, PDGFR, VEGFR	3
AMG 706	KIT and VEGFR	2
Bevacizumab	VEGF	2
BAY43-9006 (sorafenib)	Ras/raf, VEGFR	2
BMS-354825	KIT and Abl	1
RAD001	mTOR	1
PKC412	PI3 kinase	1

The phase 1 and 2 trials of SU011248 in patients who had imatinib refractory GISTs or imatinib intolerance treated 97 patients, 96% of whom had progressed on a dose of 600 mg or higher of imatinib [62,63]. Most patients had extensive metastases. PET scan noted decreased metabolic activity after 7 days of therapy, with CT scan responses evolving more slowly. To date, the PR rate is 8% with an additional 58% of patients having SD using RECIST criteria. The duration of tumor response had not been reached with a median follow-up time of 12 months. What was of particular interest was the response and clinical benefit observed in patients who have mutations that are less sensitive to imatinib, such as exon 9, wild-type *KIT*, and *PDGFR-α*, and those who have acquired mutations identified with the development of resistance (Table 5). This agent is currently in a phase 3 double-blind, placebo-controlled trial in patients who have imatinib-refractory GISTs or patients who are intolerant to imatinib. The primary endpoint of the study is to compare the time to tumor progression in patients treated with SU011248 to those receiving the best supportive care.

Other tyrosine kinase inhibitors

AMG706 is a tyrosine kinase inhibitor with specificity against KIT and VEGFR. An ongoing phase 2 trial is testing its efficacy in patients who have progressed on imatinib. BMS 354,825 [N-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide] is an Src-family kinase inhibitor. It has undergone preclinical testing in a mouse model of chronic myelogenous leukemia refractory to imatinib mesylate because of the structural similarities between Abl and Src, particularly in the setting of mutations seen in the Bcr-Abl gene in patients who became refractory to imatinib [65,66]. Animals treated with BMS 354,825 had a prolonged survival compared with untreated animals. A phase 1 trial of the agent has revealed responses in 31 of 36 patients who had imatinib refractory CML or

Table 5
Response to treatment based on c-Kit and platelet-derived growth factor receptor genotype

Drug	Mutation	N	RECIST response	Clinical benefit[a]
Imatinib [64]	Exon 11	85	83.5%	NA
	Exon 9	23	47.8%	NA
	WT KIT or PDGFR	9	0%	NA
SU011248 [63]	Exon 9	15	40%	80%
	Single PDGFR	1	0%	100%
	WT KIT or PDGFR	9	11%	55%
	2nd mutation exon 13 or 14	16	13%	56%
	KIT exon 11	7	0%	14%
	KIT exon 17	8	0%	38%

Abbreviation: NA, not available.

[a] RECIST-defined response + stable disease.

imatinib intolerance [66]. An ongoing phase 1 trial is evaluating efficacy in patients who have GISTs and other solid tumors.

Combination therapies

GIST tumors are vascular tumors. Immunohistochemistry has identified evidence of VEGF in GISTs, and patients who have metastatic tumors have been shown to have elevated serum VEGF (vascular-endothelial growth factor) levels [67]. A hypothesis based on the data of the SU011248 trial is that one important mechanism of disease control is the anti-VEGFR inhibition. Therefore, a phase 3 trial will be testing the combination of Bevacizumab, a fully humanized monoclonal antibody that binds VEGF, in combination with imatinib. In evaluating the pathway through which KIT and PDGFR signal, there are multiple other targets that could be inhibited. For example, RAD001, an inhibitor of the mammalian target of Rapamycin, is being added to imatinib [60]. RAD001 is a member of the phosphatidylinositol kinase–related kinase family in which a lipid kinase homology domain functions as a serine/threonine kinase to regulate protein translation, cell cycle progression, and cellular proliferation. The initial results have shown significant pharmacokinetic interactions between the two agents with increases in the serum concentration of RAD001 when given concurrently with imatinib, but no significant activity to date. Another agent that is being tested is PKC412, an oral staurosporine derivative that has activity against multiple kinases, including protein kinase C isotypes a, b, and g; KIT (WT and mutated); PDGFR-α and -β, VEGFR2, FGFR (fibroblast growth factor receptor), and FLT3 [61]. Pharmacokinetic studies of the combination of the effects of PKC412 when added to imatinib revealed up to 70% decreases in serum concentrations of imatinib. In contrast, when imatinib was added to PKC412, there was an increase in serum levels of PKC412 and increased toxicity. To date, three of 17 evaluable patients have stable disease. The phase 1 trial of this combination is ongoing to define the appropriate phase 2 doses.

Summary

The management of GISTs has undergone a rapid change since the demonstrated effectiveness of treatment targeting its molecular drivers KIT and PDGFR-α. This disease, previously only well controlled by surgery, was refractory to chemotherapy. Imatinib has altered the natural history of patients who have unresectable and metastatic disease, extending their lives significantly. Ongoing clinical trials are evaluating its benefit in the adjuvant and neoadjuvant setting to determine if therapy can improve survival and resectability of tumors. In addition, newer agents are being tested in patients who have imatinib refractory disease. At present, imatinib is the only agent that is approved for use in GISTs. However, it is likely that other agents will become available. Learning to

correlate the site of *KIT* and *PDGFR-α* mutations with response will likely lead to the selection of a specific drug for a specific genotype.

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